

# Mutations of the *CYP1B1* gene in congenital anterior staphylomas

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**Purpose:** Here, we present two patients with congenital anterior staphyloma, with mutations in the *CYP1B1* gene.

**Methods:** We reviewed the medical records, including the genetic analysis.

**Results:** Two unrelated patients presented with congenital anterior staphylomas. Both patients showed mutations in the *CYP1B1* gene. The first patient, the product of a consanguineous marriage, showed a homozygous missense mutation g.3987G>A (p.G61E). The second patient had compound heterozygous missense mutations [g.4160 G>T (p.A119S) and g.8131 C>G (p.L432V)].

**Conclusion:** *CYP1B1* gene mutation may be associated with congenital anterior staphylomas.

**Keywords:** mutation analysis, congenital glaucoma, consanguinity, congenital aphakia

## Introduction

Congenital anterior staphyloma is a rare condition characterized by enlarged, opaque, ectatic corneas that protrude through the interpalpebral fissure. This congenital malformation has been described in isolated case reports, but the etiology remains unclear.<sup>1</sup> In this paper, we report two cases of congenital staphyloma that were associated with *CYP1B1* gene mutations.

## Case reports

The history, clinical findings at presentation, the clinical course, and findings after genetic testing are summarized in Table 1 and illustrated in Figures 1 and 2.

## Discussion

Congenital anterior staphyloma is a rare unilateral or bilateral anomaly and may account for about 11% of congenital corneal opacities.<sup>2</sup> The clinical findings include an enlarged, vascularized, ectatic cornea, with thinning and ectasia of the surrounding anterior segment structures. These findings are associated with marked anterior segment anomalies that can include an iris that is adherent to the posterior corneal surface or a partially absent iris. The crystalline lens may be adherent to the posterior corneal surface, similar to Peters anomaly, be subluxed, or show cataractous changes.<sup>1,3–5</sup> The degree of staphylomatous changes can be variable. In our patients, the corneal ectasia was not as conspicuous, with the staphylomatous changes being more prominent in the limbal region. Limbal staphylomas can occur due to stretching and thinning of the globe, as a result of high intraocular pressure in severe

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**Table 1** Clinical features and course of patients with congenital anterior staphylomas

Age at presentation/sex	Family history	IOP at presentation/last visit (mmHg)	Clinical features	Condition at last visit at 6 yrs of age	Genetic studies
<b>Patient 1</b>					
Birth/male	Parents first cousins; no other affected family members	18/18	VA: fixes and follows both eyes Buphthalmia OU Cloudy, ectatic corneas with ill-defined limbus; corneal diameters approximately 15 mm OD and 14 mm OS Iris adherent to cornea Circumferential limbal staphylomas; dislocated lens in vitreous	VA: HM OD, CF I foot S; eye exam unchanged since birth Treated with 0.5% timolol maleate OU	P450 ( <i>CYP11B1</i> ) gene: Homozygous missense mutation g.3987G>A (p.G61E) in patient The same mutation in both parents in a heterozygous state
<b>Patient 2</b>					
Birth/male	Parents not related; no other affected family members	16.5 OD; 16 OS/16 OD; 20 OS	VA: fixes and follows; left eye more severely affected Enlarged ectatic corneas with scarring and vascularization OU Ill-defined staphylomatous limbus OU Iris adherent to cornea OU Congenital aphakia OU	VA: HM OU; condition unchanged since first presentation Treated with 0.5% timolol maleate and 0.5% apraclonidine OU	P450 ( <i>CYP11B1</i> ) gene: Compound heterozygous missense mutations [g.4160 G>T (p.A119S) and g.8131 C>G (p.L432V)] Father had g.8131 C>G mutation in a heterozygous status. DNA not available from the mother for genetic testing

**Abbreviations:** CF, counting fingers; DNA, deoxyribonucleic acid; HM, hand motions; IOP, intraocular pressure; OD, right eye; OS, left eye; OU, both eyes; VA, visual acuity.

**Figure 1** Patient 1.

**Notes:** Top: note the bilateral opacified, ectatic corneas, with protrusion of the globe and limbal staphylomas. Bottom left: UBM showing iris adherent to the posterior corneal surface (arrow) and absence of the crystalline lens (horizontal axial scan). Bottom right: T2 MRI bilateral large globes with dislocated lenses in the vitreous cavity (arrowheads). Dilation of the optic nerve sheath in the peripapillary region, suggestive of optic nerve hydrops, is noted.

**Abbreviations:** MRI, magnetic resonance imaging; UBM, ultrasound biomicroscopy.

**Figure 2** Patient 2.

**Notes:** Top: color photograph of the right eye, showing an ectatic vascularized cornea, with corneal/limbal staphylomas. Bottom left: UBM showing the iris adherent to the posterior corneal surface (arrow) and absence of the crystalline lens (radial scan with angle at 9 o'clock). Bottom right: T2 MRI showing bilateral enlarged globes with aphakia. Dilation of the optic nerve sheath in the peripapillary region, suggestive of optic nerve hydrops, is noted.

**Abbreviations:** MRI, magnetic resonance imaging; UBM, ultrasound biomicroscopy.

congenital glaucoma. The clinical course in such patients is progressive, often requiring multiple surgical interventions. In contrast, our patients presented at birth with severe anterior segment changes that remained stable and mild-to-moderate intraocular pressure elevations that appeared controlled with medications. In the differential diagnosis, the pathologies considered included severe primary congenital glaucoma with anterior segment dysgenesis and Peters anomaly.<sup>2</sup> There seems to be considerable overlap in the clinical features between these clinical conditions.<sup>6</sup> Though the presenting conditions could be considered as a severe form of anterior segment dysgenesis, it was felt that the term was generic since both patients had phenotypic features that were more consistent with those seen in congenital anterior staphylomas. Peters anomaly presents with central corneal opacities with thinning, and with iris adhesions to the posterior surface. Corneal ectasia, staphylomas, and adherence of the crystalline lens have been reported in cases of Peters Plus syndrome with multiple systemic abnormalities.<sup>7,8</sup> Both patients in this study showed corneal opacification, ectasia, and vascularization. In addition, our first patient had a dislocated crystalline lenses and the second patient had had congenital aphakia, both of which have been described with Peters anomaly and congenital anterior staphylomas.<sup>9,10</sup>

Multiple etiological factors have been implicated in the pathogenesis of congenital anterior staphylomas. These include intrauterine infections and specific chromosomal abnormalities with multisystem organ involvement, and an association with amniotic band syndrome has been reported.<sup>3,9,11</sup> However, in most cases, the etiology remains undetermined. Both our patients had no family history; however, patient 1 was the product of a consanguineous marriage, alerting us to further look into the association of *CYP1B1* mutations with the anterior staphylomas.

We detected a homozygous *CYP1B1* mutation g.3987G>A (p.G61E) in patient 1. This mutation is the most common mutation in Saudi Arabian patients with primary congenital glaucoma.<sup>12</sup> The mutation was inherited in a homozygous status and was heterozygous in both parents, thus fits well with the fact that both parents were first cousins. A previous study attempting to correlate this mutation with a particular phenotype was unsuccessful.<sup>11</sup> This mutation was previously described in Saudi patients with familial juvenile open-angle glaucoma,<sup>13</sup> in Peters anomaly,<sup>14</sup> and in isolated open-angle glaucoma.<sup>15</sup>

As for patient 2, he carried compound heterozygous mutations, g.4160 G>T (p.A119S) and g.8131 C>G

(p.L432V), which were inherited from his father. Unfortunately, deoxyribonucleic acid (DNA) was not available from the mother, but it is likely that she harbored the other mutation detected in her son. This was consistent with the history that both parents were not related. Both mutations (p.A119S and p.L432V) are less common than the p.G51E, and mutational phenotypes have not been described with the phenotype seen in the two affected patients. Two *CYP1B1* mutations detected in our patients (p.G61E and p.A119S) had an established pathogenicity.<sup>12</sup> As for the L432V, the literature is inconclusive about its pathogenic role as this mutation has been detected in normal Turkish and Japanese populations, in a heterozygous status with no other mutation in the *CYP1B1* gene.<sup>16</sup> It is plausible to suggest that this mutation, if inherited in a heterozygous status with no other *CYP1B1* mutation, may not cause the development of congenital glaucoma. However, if this mutation is inherited in a homozygous status or in a heterozygous status with another *CYP1B1* mutation, then it may be capable of causing the disease.

Homozygous/compound heterozygous mutations in the *CYP1B1* gene are typically associated with primary congenital glaucoma.<sup>17</sup> Several reports have identified *CYP1B1* mutations in patients with other phenotypes, such as isolated Peters or Axenfeld-Rieger anomaly. These phenotypes are typically associated with glaucoma.<sup>14,18</sup> Homozygous or compound heterozygous *CYP1B1* mutations were identified in eight probands with mild ectropion uvea, partial aniridia, and congenital glaucoma,<sup>19</sup> and now this report further expands the ocular phenotype associated with *CYP1B1* mutations.

## Disclosure

The authors report no conflicts of interest in this work.

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